

Global vaccine safety blueprint

Immunization, Vaccines and Biologicals



World Health
Organization

Global vaccine safety blueprint

Immunization, Vaccines and Biologicals



**World Health
Organization**

**The Department of Immunization, Vaccines and Biologicals
thanks the Bill and Melinda Gates Foundation
whose financial support has made the production
of this document possible.**

This document was published by the
Quality, Safety and Standards unit
of the Department of Immunization, Vaccines and Biologicals

Ordering code: WHO/IVB/12.07

Printed: February 2012

This publication is available on the Internet at:

www.who.int/vaccines-documents/

**Copies of this document as well as additional materials on
immunization, vaccines and biologicals may be requested from:**

World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland

• *Fax:* + 41 22 791 4227 • *Email:* vaccines@who.int •

© World Health Organization 2012

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; email: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

The named authors alone are responsible for the views expressed in this publication.

Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

<i>Glossary</i>	<i>v</i>
<i>Acknowledgements</i>	<i>vii</i>
<i>Abbreviations & acronyms</i>	<i>ix</i>
 Part 1: The Global Vaccine Safety Blueprint	1
Mission, vision and goals	1
<i>Mission</i>	<i>1</i>
<i>Vision</i>	<i>1</i>
<i>Strategic Goals</i>	<i>1</i>
 Background	5
<i>Purpose and scope of this document</i>	<i>5</i>
<i>A changing landscape of vaccine use</i>	<i>6</i>
<i>A changing landscape for vaccine safety</i>	<i>7</i>
<i>Communicating about vaccine safety</i>	<i>7</i>
<i>Medicines and vaccines</i>	<i>8</i>
<i>Taking advantage of global resources</i>	<i>9</i>
<i>Situation analysis</i>	<i>9</i>
 Part 2: Objectives	11
 Objective 1: To strengthen vaccine safety monitoring in all countries	11
1.1 <i>Rationale for action</i>	<i>11</i>
1.2 <i>Targets and outputs</i>	<i>12</i>
 Objective 2: To strengthen the ability of countries to evaluate vaccine safety signals	16
2.1 <i>Rationale for action</i>	<i>16</i>
2.2 <i>Targets and outputs</i>	<i>17</i>
 Objective 3: To develop vaccine safety communication plans at country level, to promote awareness of vaccine risks and benefits, understand perceptions of risk and prepare for managing any adverse events and concerns about vaccine safety promptly	19
3.1 <i>Rationale for action</i>	<i>19</i>
3.2 <i>Targets and outputs</i>	<i>20</i>

Objective 4: To develop internationally harmonized tools and methods to support country vaccine safety activities	22
4.1. <i>Rationale for action.....</i>	22
4.2. <i>Targets and outputs.....</i>	23
Objective 5: To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels	25
5.1 <i>Rationale for action.....</i>	25
5.2 <i>Targets and outputs</i>	26
Objective 6: To strengthen regional and global technical support platforms that meet countries' expressed needs	28
6.1 <i>Rationale for action.....</i>	28
6.2 <i>Targets and outputs</i>	29
Objective 7: To provide expert advice on vaccine safety issues at national, regional and international levels	31
7.1 <i>Rationale for action.....</i>	31
7.2 <i>Targets and outputs.....</i>	32
Objective 8: To put in place systems for appropriate interaction between national governments, multilateral agencies and manufacturers at national, regional and international levels	33
8.1 <i>Rationale for action.....</i>	33
8.2 <i>Targets and outputs.....</i>	34
Part 3: Framework for implementation.....	35
Implementation of the Global Vaccine Safety Blueprint	35
<i>Introduction.....</i>	35
<i>Function and institutional base</i>	35
<i>Global Vaccine Safety Initiative — a minimal structure</i>	36
<i>Workplan.....</i>	37
<i>Relationship with industry.....</i>	37
<i>New collaborators.....</i>	37
Annex: What is an adverse event following immunization (AEFI)?.....	38

Glossary

Prequalification

Prequalification is the procedure for assessing the acceptability of medicines, diagnostics and vaccines for purchase by the United Nations. Information on the prequalification of vaccines can be seen on the WHO web site at http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/index.html.

Signal (safety signal)

The Council for International Organizations of Medical Sciences (CIOMS) has defined a signal as “information (from one or multiple sources) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifactory action.” A signal is therefore a hypothesis, together with data and arguments.

Surveillance

Systematic ongoing collection, collation and analysis of data and the timely dissemination to those who need to know the information so that action can be taken. The data-collection method determines the type of surveillance, so that:

- passive surveillance is based on passive reporting;
- stimulated surveillance is based on stimulated reporting;
- active surveillance is based on systematic search for cases.

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. Examples of active surveillance are, cohort studies that have been conducted in the United States of America, the United Kingdom, Denmark and others, to evaluate the safety of vaccines, in which all outcomes for specified events are identified in a predefined cohort using clinical information databases. Using such systems it is possible to ascertain events in a population completely, and in an unbiased manner, which facilitates accurate assessment of any potential safety issues.

Vaccine pharmacovigilance

The science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues. Explanatory notes on this definition can be found at http://www.cioms.ch/activities/frame_vaccpharmadef.htm.

The term “enhanced capacity” for vaccine pharmacovigilance is used in the Blueprint in contrast to minimal pharmacovigilance capacity. Enhanced vaccine pharmacovigilance, at a minimum level, includes improved data collection, in passive surveillance, towards higher data quality and more complete data sets, but also improved collation, verification, analysis and communication by building capacity for stimulated and active surveillance. It also includes the ability to perform population-based studies and appropriate epidemiologic studies testing hypotheses by assessing relative and absolute risk ratios, when appropriate.

Acknowledgements

The development of the Blueprint, including its landscape analysis (WHO/IVB/12.04), was supported by a grant from the Bill and Melinda Gates Foundation.

David Bramley wrote this document with guidance from a Collaborative Group composed of Steve Black, Jan Bonhoeffer, Alex Doodoo, Juhani Eskola, Heidi Larson, Stanley Plotkin, Sunheang Shin and the WHO secretariat.

The Blueprint and its strategies benefitted from multiple inputs, including but limited to all participants in the surveys of vaccine safety experts, regulators and vaccine manufacturers, all participants in the Global Vaccine Safety Meeting that took place at WHO headquarters on 26 and 27 September 2011, colleagues responsible for quality and safety of vaccines in WHO regional offices and from the Departments of Immunization, Vaccines and Biologicals and Essential Medicines and Health Products.

Throughout the development process, members of the Global Advisory Committee on Vaccine Safety (GACVS) provided advice and support on the development of this plan.

WHO would like to express its sincere thanks to all contributors for their support and judicious advice.

Abbreviations & acronyms

AEFI	adverse event(s) following immunization
ARC	AEFI expert review committee
CIOMS	Council for International Organizations of Medical Sciences
DTaP	diphtheria tetanus and acellular pertussis (vaccine)
DTwP	diphtheria tetanus and whole-cell pertussis (vaccine)
ECBS	Expert Committee for Biological Standardization
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization)
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	individual case safety report
IHR	International Health Regulations
IPAC	Immunization Practices Advisory Committee
IPV	inactivated poliovirus vaccine
LMIC	low- and middle-income countries
NRA	national regulatory authority
OPV	oral polio vaccine
SAGE	Strategic Advisory Group of Experts (on Immunization)
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Part 1:

The Global Vaccine Safety Blueprint

Mission, vision and goals

Mission

To optimize the safety of vaccines through effective use of pharmacovigilance principles and methods.

Vision

Effective vaccine pharmacovigilance systems are established in all countries.

Strategic Goals

- To assist low and middle income countries (LMIC) to have at least minimal capacity for vaccine safety activities.
- To enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines.
- To establish a global vaccine safety support structure.

Goals in detail

Minimal capacity at country level

Minimal capacity for vaccine safety draws on the model proposed for other pharmacovigilance activities¹. It includes:

- a national dedicated vaccine pharmacovigilance capacity, with designated staff for this purpose, stable basic funding, clear mandates and well-defined structures and roles, collaborating with the WHO Programme for International Drug Monitoring;
- health-care workers and others encouraged to report vaccine safety issues;
- a reporting form for individual case safety reports (i.e. a national reporting form for AEFI)²;

¹ GFATM, WHO. Minimum requirements for a functional pharmacovigilance system. Geneva, Global Fund to fight AIDS, Tuberculosis and Malaria and World Health Organization, 2010 (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2_en.pdf).

² See the Annex for general and cause-specific definitions of an adverse event following immunization (AEFI).

-
- a national database or system for collating, managing and retrieving AEFI reports;
 - a national AEFI expert review committee (ARC) that is able to provide technical assistance on causality assessment of serious AEFI, and clusters of AEFI, so that unwanted risk can be managed;
 - a clear strategy for risk communication that identifies risks and benefits to prepare health professionals, caregivers and the public for possible vaccine reactions, by explaining possible coincidental events, encouraging the monitoring of AEFI by all concerned, and with preparedness plans in place to address vaccine safety crises (risk communication is dynamic and needs a feedback loop to all relevant stakeholders);
 - implemented and harmonized methods and tools for the monitoring and investigation of AEFI.

In this plan, the minimal capacity for vaccine safety is strengthened by a number of managerial elements that guarantee its functionality, namely:

- a regulatory framework is in place that defines the provisions for monitoring and management of AEFI;
- clear lines of accountability have been identified for the conduct of vaccine safety work;
- an institutional development plan is in place for implementation of activities and development of performance indicators;
- the institutional development plan is periodically evaluated and revised in order to ensure continuous quality improvement when conducting national vaccine safety activities;
- there is a commitment to sharing information on vaccine safety with other countries.

Enhanced capacity: an increased level of vaccine safety activity

Spontaneous reporting systems are insufficient to enable rapid assessment and adequate public- health response to vaccine safety signals. Rapid response to vaccine safety signals is required to identify those rare instances where real adverse reactions occur, so that their impact can be minimized as they emerge. Countries where an increased level of vaccine safety activity is judged to be necessary, are those where newly-developed vaccines are being introduced and in countries that manufacture and use prequalified vaccines. In addition to the basic and managerial requirements for minimal capacity, the enhanced capacity for vaccine safety activity will include the following:

- the ability to carry out active surveillance rather than relying solely on spontaneous reporting of AEFI alone for the purpose of signal detection;
- the ability to carry out epidemiological studies to test hypotheses.

International collaboration and strategic planning

Over the years, many institutions throughout the world have developed expertise in implementing vaccine pharmacovigilance and supporting immunization programmes for the purpose of safety. Those organizations, in academia, research groups and technical agencies, as well as the health authorities of several countries (immunization programmes, pharmacovigilance centres or regulatory agencies), provide international support in order to assist other countries develop their capacity for vaccine pharmacovigilance. The success of the proposed initiative to enhance national vaccine safety systems will depend upon establishing a collaborative support structure with all those organizations. This collaborative structure will, in particular, be a resource to:

- foster regional and international sharing of vaccine safety data through the development of tailored solutions that will build on existing national systems;
- build a decentralized investigational capacity and facilitate sharing of information;
- build networks of experts to assist countries in strengthening vaccine safety programmes, in particular through training, and in carrying out investigations of vaccine safety signals;
- establish centres of excellence in order to support capacity-building initiatives and crisis responses in geographical proximity to all countries;
- ensure that sufficient and effective pharmacovigilance is available whenever a newly-available vaccine is being introduced;
- provide advice on important vaccine safety issues through national, regional and global expert advisory groups;
- exchange information with vaccine manufacturers to monitor and maintain up-to-date vaccine safety profiles.

Implementation of the goals

In order to achieve the three goals described above, the Global Vaccine Safety Blueprint has eight objectives that, together, aim to build and support effective vaccine pharmacovigilance in all low- and middle-income countries and promote a systemic approach to so doing. Objectives 1 to 4 relate directly to the components of vaccine pharmacovigilance, while objectives 5 to 8 relate to supporting elements that must be in place for the vaccine safety system to function effectively. The eight objectives are as follows.

- Objective 1:* To strengthen vaccine safety monitoring in all countries.
- Objective 2:* To strengthen the ability of countries to investigate vaccine safety signals.
- Objective 3:* To develop vaccine safety communication plans at country level to promote awareness of vaccine risks and benefits, understand perceptions of risk and prepare for managing any adverse events and concerns about vaccine safety promptly.
- Objective 4:* To develop internationally harmonized tools and methods to support country vaccine safety activities.

-
- Objective 5:* To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels.
- Objective 6:* To strengthen regional and global technical-support platforms that meet countries' expressed needs.
- Objective 7:* To provide expert advice on vaccine safety issues at national, regional and international level.
- Objective 8:* To put in place systems for appropriate interaction between national governments, multilateral agencies and manufacturers at national, regional and international level.

The eight objectives listed here, and described in Part 2, are based on wide experience of vaccine pharmacovigilance globally, including in LMIC. In many of these latter countries, vaccine pharmacovigilance is limited, and in some places non-existent, yet experience has shown that it can be achieved with high-level commitment and by seizing key opportunities — such as the introduction of new vaccines that have never before been given on such a large scale.

The description of each objective begins with the rationale for action in that specific area, and also includes the targets that must be fulfilled and a summary of the outputs that are planned.

Background

Purpose and scope of this document

Vaccines are administered in order to save lives and preserve health. They are among the safest medicinal products and are administered to healthy individuals, including to very young children. However, a small minority of persons who are vaccinated may experience reactions to the vaccine, most of which are mild and time-limited but can also, in rare cases, have significant impact on health. Fear of vaccine reactions, real or perceived, deters many people from undergoing vaccination. The problems of vaccine reaction and reluctance to be vaccinated have been known for many years in industrialized countries and is often raised after most of the benefits from immunization have been obtained with the disappearance of several diseases. As immunization programmes have expanded in LMIC in recent decades, the problems have become more familiar there too. The Global Vaccine Safety Blueprint was drawn up to help protect people globally by providing LMIC with a set of options for ensuring safe use of vaccines, and for deriving maximum benefit from them. The Blueprint proposes strategic goals that will be achieved through a Global Vaccine Safety Initiative. This Initiative is a truly collaborative international effort, hosted by WHO, that focuses on assisting all countries in making sure that vaccines do what they are supposed to do — protect all of us, and especially our children, from sickness and ill-health in the safest possible way.

In 2005, the Global Immunization Vision and Strategy 2006–2015 was developed to define how WHO, UNICEF and their partners should engage in furthering the benefits that can be derived from the use of vaccines.³ There are many aspects to ensuring vaccine safety — during research, production, packaging, transport, storage and administration of the vaccine, and after use — and a range of governmental, nongovernmental and commercial bodies are involved in vaccine safety worldwide.⁴ The Global Vaccine Safety Blueprint focuses on vaccine safety after a product has been licensed for use and, in particular, on the need to monitor vaccinated populations for the occurrence of adverse events following immunization (AEFI) and to address vaccine safety concerns when they arise. Currently, this takes place in most developed countries and in some developing ones, but by no means everywhere. The capacity to monitor for vaccine safety and to investigate potential problems varies considerably between countries. In some cases, this capacity is very limited indeed, yet recent experience with the introduction of new vaccines has highlighted the need to have effective safety monitoring of vaccines in place.

The Global Vaccine Safety Blueprint is not the first document to draw attention to the need for improved global “vaccine pharmacovigilance.” Several organizations and partners, including WHO, UNICEF, GAVI and many international technical agencies, are involved in various aspects of vaccine pharmacovigilance either directly or indirectly. As a set of global strategies, however, the Global Vaccine Safety Blueprint represents an attempt to leverage international commitment and to set out a framework for coordinated action that will raise the level and accuracy of vaccine safety monitoring globally, and will enable cases of AEFI to be investigated wherever they occur.

³ WHO and UNICEF. Global Immunization Vision and Strategy 2006–2015 (WHO/IVB/05.05). Geneva, World Health Organization and New York, NY, United Nations Children’s Fund, 2005.

⁴ Dellepiane N, Griffiths E, Milstein J. New challenges in assuring vaccine quality. Bulletin of the World Health Organization, 2000, 78(2):155–162.

A substantial proportion of AEFI results from inadequate handling and administration. Strategies to ensure safe programmatic usage of vaccines are devised by immunization programmes. They are not addressed in this document that focuses on the effects related, or believed to be related, to the vaccine product themselves. Separate guidance documents are available to address vaccine management and immunization techniques, in particular from WHO.^{5,6}

A changing landscape of vaccine use

Large-scale immunization programmes now reach unprecedented numbers of people in developing countries.⁷ The number of vaccine doses administered worldwide keeps increasing as new vaccines are developed and are made available and more people have access to vaccines. Although vaccines have shown themselves to be both effective and cost-effective in improving human health, immunization programmes need to be backed by reliable safety measures.⁸ The United Nations system purchases more than half of all vaccine doses produced worldwide. In 2007, for example, UNICEF alone purchased 3.2 billion vaccine doses.⁹

Unlike in the past, some of these newly-developed vaccines are made available to people in LMIC at the same time as in developed countries. The development of further important vaccines, such as those against dengue, HIV, malaria and tuberculosis — of primary interest for use in low-income countries — will make the challenge even more acute, since these vaccines have never previously been used anywhere. Some of these vaccines may use new technological approaches (e.g. multiple proteins, DNA, RNA or recombinant viral vectors) with little past human use experience. Thus, children and adults in LMIC are, for the first time, being given vaccines without the benefit of prior experience elsewhere. In addition, those populations include many special groups, in particular high rates of HIV prevalence, malnutrition and other diseases, or pregnancy, where the safety profile of these new vaccines may differ.

The years leading up to 2020 have been designated the Decade of Vaccines. This initiative, which was launched in 2010, aims to increase coordination across the vaccine community worldwide and to create a global vaccine action plan. The Decade of Vaccines initiative has issued a call to action that comprises four elements: intensified research and development, advocacy at the highest level, increased compliance and shouldering of responsibilities by developing countries, and an expanded effort in communicating the benefits of vaccines.¹⁰ The Global Vaccine Safety Blueprint will contribute to the Decade of Vaccines by optimizing the safety of delivered vaccines.

⁵ World Health Organization. Injection safety (http://www.who.int/injection_safety/en/index.html).

⁶ World Health Organization. Vaccine management and logistics (http://www.who.int/immunization_delivery/systems_policy/logistics/en/index.html).

⁷ Horton R, Das P. The vaccine paradox. *The Lancet*, 9 June 2011 (Early online publication; doi:10.1016/S0140-6736(11)60765-4).

⁸ Duclos P. A global perspective on vaccine safety. *Vaccine*, 2004, 22:2059–2063.

⁹ WHO, UNICEF, the World Bank. State of the world's vaccines and immunization, 3rd ed. Geneva, World Health Organization, 2009 (http://www.unicef.org/immunization/files/SOWVI_full_report_english_LR1.pdf).

¹⁰ Moxon ER et al. A call to action for the new decade of vaccines. *The Lancet*, 9 June 2011 (Early online publication; doi:10.1016/S0140-6736(11)60766-6).

A changing landscape for vaccine safety

Situation-analysis research, conducted in support of the Global Vaccine Safety Blueprint, shows that countries and their partners generally have high awareness of the need to improve vaccine safety systems. Yet the situation analysis also confirms that only a small proportion of LMIC have functional vaccine safety systems and few provide global reporting or investigation of AEFI. Where there is routine vaccination of the population by adequate and accessible medical services, it should be possible, at a minimum, to establish a system for the reporting of AEFI. Such a system will depend upon the readiness of the vaccine recipient (or his/her relatives) to report a potential problem, the readiness of health workers to report what may often seem to be minor events, and the capacity of national authorities to collate and analyse the reports and to take action on them.

While some developing countries are recipients of vaccines, others produce vaccines, both for their own internal use and for export, often to other developing countries. WHO will not prequalify vaccines unless the producing country has a functioning national regulatory authority (NRA) and there is a thorough verification of compliance with specifications.¹¹ Where safety-systems exist, these usually consist of spontaneous (passive) reporting for most circumstances. Due to the limitations of spontaneous AEFI reporting, these systems are not sufficient to monitor newly available vaccines in a timely fashion. Although AEFI are monitored in pre-licensure studies, where thousands to tens of thousands of people are involved, the number of people who will receive the vaccines after licensing is usually in the range of millions. It is only after licensing that very rare AEFI may therefore be detected and corrective action taken, provided that adequate monitoring systems are in place. Countries that will benefit from early use of those promising vaccines should have an expanded vaccine pharmacovigilance capacity to conduct active surveillance. When serious AEFI are detected, their causal relation to the specific vaccine needs to be investigated. In a significant number of cases, the vaccine product has no bearing on the events reported. When safety signals are detected through the surveillance systems in place, these should drive the development of epidemiological studies, to qualify possible risks and measure their magnitude. This additional attention to safety is required so that any possible unwanted reactions to the new products can be effectively identified and characterized before the vaccines are used in countries with weaker pharmacovigilance systems.

Communicating about vaccine safety

Any AEFI monitoring system also needs capacity to manage and respond promptly to public concerns about vaccine safety. Public concerns arise because people want to avoid damage to their health. Rather than wait for concerns to arise, it is important that children and their parents are educated to understand how vaccination helps them to avoid health damage. Teachers and health workers have a role to play in this, as do leading community figures. Vaccine safety communication is not just a matter of responding to rumours; it involves helping society to recognize the importance of vaccination to human health.

¹¹ Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/IVB/05.19). Geneva, World Health Organization, 2005.

As the performance and visibility of immunization programmes improves, many parts of the world have also witnessed the emergence of anti-vaccine movements that emphasize possible health risks linked to vaccine use. Anti-vaccination groups may exaggerate the dangers, and the media may report the situation in a way that is not scientifically accurate. Such a situation can lead to a fear of vaccines that discourages people from being vaccinated and promotes the spread of disease.¹² In addition, some traditional vaccine-preventable diseases are disappearing, leading to low perception of risk by some members of the public who may assume that vaccination is no longer necessary. Improving access to risk-communication tools is thus urgent in many LMIC.¹³

Communication measures alone are insufficient as a public-health response for many vaccine safety concerns, unless they are complemented by investigative action. In the past, major immunization campaigns have been delayed or halted due to slowness in detecting a serious vaccine safety concern, or because of misinformation spreading when there was no safety monitoring in place to show the real situation. AEFI should be investigated as promptly as possible while still allowing for reaching meaningful conclusions. Public concerns must be carefully monitored and managed in the interim. In the absence of vaccine pharmacovigilance, unfounded vaccine safety scares can threaten successful vaccine programmes.

Medicines and vaccines

Although the use of vaccines is very different from the use of medicines, some of the same safety principles apply, and some of the same institutions (such as the NRAs) are involved. Understanding commonalities and differences between the practice of pharmacovigilance for medicines and vaccines helps to design better safety systems that can address the specific needs of vaccines. One important difference is that most medicines are generally used to treat or control diseases among those who have health problems, while vaccines are usually administered to large numbers of healthy people in order to prevent diseases. Since vaccine recipients are generally healthy, there is a lower level of tolerance for the risk of a side-effect, as compared to medications. Where vaccination is mandatory, or where the fear of the disease itself has disappeared because of the very effectiveness of vaccines, the tolerance to AEFI tends to be even lower. When vaccines are given to children, the tolerance to risk is lower still. Thus, a much higher standard of safety is expected of vaccines.

In the area of pharmacovigilance for medicines, the focus is on the reporting, assessment and prevention of adverse reactions following the use of drugs that are most frequently used to treat illnesses. WHO, the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) and other agencies involved in pharmacovigilance have already outlined the minimum functions of a national pharmacovigilance system in terms of: collecting and managing reports of adverse drug reactions; identifying signals for drug safety and quality problems; communicating effectively; carrying out risk assessment; maintaining information on medicine prescribing and use, and ensuring that information from pharmacovigilance benefits other health programmes.

¹² Chen RT et al. Challenges and controversies in immunization safety. *Infectious Disease Clinics of North America*, 2001, 15:21–39,

¹³ Larson HJ et al. Addressing the vaccine confidence gap. *The Lancet*, 9 June 2011 (Early online publication; doi:10.1016/S0140–6736(11)60678–8).

Taking advantage of global resources

Various organizations and institutions are active in vaccine safety at global and regional levels.¹⁴ However, the landscape analysis conducted for the Blueprint has revealed an uneven coverage of needs, both locally and internationally with, so far, no consistent attempt to synergize the activities of various stakeholders. Efforts to strengthen vaccine safety in LMIC should include the valuable approaches that already exist globally, in order to avoid duplication and overlap. Key stakeholders in this initiative include national regulators and immunization programmes, vaccine manufacturers, technical agencies, vaccine safety experts (from academia and elsewhere) and donors, and may also be the product of collaboration between several groups.

Providing additional attention to the safety of newly-available vaccines requires strategic planning for their introduction, and support from international infrastructures to promote sound and consistent methodological approaches as well as adequate exchange of information. The Blueprint focuses on how national and international players can better collaborate in filling current gaps in vaccine pharmacovigilance and management and communication infrastructure, and better prepare for vaccine use that prevents avoidable AEFI. There are no one-size-fits-all recommendations, but best practices exist that can be adapted to a range of national situations. Achieving the objectives of the Blueprint will require different approaches to implementation and different resources in different places.

Situation analysis

The Global Vaccine Safety Blueprint draws on the findings of a situation analysis of the vaccine safety infrastructure in low-income countries which was carried out during 2010. That situation analysis set out to:

- assess local capacity for vaccine safety systems in the poorest countries, identify the needs for establishing vaccine safety monitoring in those countries and obtain an inventory of existing global or intercountry vaccine safety initiatives;¹⁵
- determine how global and intercountry resources for vaccine safety can best contribute to a global effort to address the needs identified at country level and identify possible synergies among those initiatives;¹⁶
- assess availability of vaccine safety data to regulators from manufacturing and procuring countries, understand systems in place regarding vaccine safety from the perspective of the licensing authorities and document their expectations regarding the proposed global vaccine safety consortium;¹⁷

¹⁴ Global Advisory Committee on Vaccine Safety (GACVS); WHO Secretariat. Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. Expert Review of Vaccines, 2009, 8:705–716.

¹⁵ Li Y et al. The capacity and needs of post-marketing vaccine safety monitoring in low- and middle-income countries. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

¹⁶ Weibel D et al. Enhanced strength-weakness-opportunity-threat analysis of international vaccine safety activities. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

¹⁷ Graham J et al. Survey of regulators. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

-
- provide information regarding post-marketing data availability from vaccine manufacturers, describe existing models of public–private collaborations regarding public-safety issues and gauge industry perspective for their role in the proposed consortium;¹⁸
 - perform a baseline assessment of the vaccine safety monitoring system in 11 low- or middle-income countries;¹⁹
 - provide a systematic analysis of performance indicators of national vaccine safety systems (using the pre-established indicators from WHO assessments of NRAs) and characterize the patterns of performance gaps by groups of countries;²⁰
 - outline the budget of existing vaccine safety initiatives and of a sample of national vaccine safety systems, and document their current funding mechanisms in order to obtain empiric financial parameters that will be used to develop a budget.²¹

The situation analysis yielded considerable data that have been used to shape the plans and activities for implementing each specific objective in the Blueprint. The situation analysis confirmed that vaccine safety is a real concern in LMIC and that there is a need in many places to improve the structures and effectiveness of vaccine safety systems. Although various tools and methodologies are available, there are few global standards and many countries have gaps in their vaccine safety systems. In addition, while a number of organizations are active internationally in vaccine safety, there is no overall coordination of their activities, leading to some overlap between them and gaps in the services provided.

With regard to the vaccine industry, the situation analysis indicated a need for up-to-date and harmonized standards for manufacturers' vaccine safety activities that can meet evolving national and international regulatory requirements. The set of studies also revealed a need for more expertise and tools in the area of risk communication in order to further transparency, avoid misunderstandings, prevent confusion and misinformation and avert anti-vaccination campaigns. These, and other elements of the situation analysis, are reflected in the Global Vaccine Safety Blueprint.

The aim of the Blueprint is to build on what already exists, in order to strengthen vaccine safety systems so that vaccines can be provided to people in all parts of the world with adequate assurance that unnecessary risks can be avoided.

¹⁸ Achkasova E et al. Survey of vaccine manufacturers. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

¹⁹ Mirzayeva R. Baseline assessment of the vaccine safety systems in the WHO global post-marketing surveillance network countries. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

²⁰ Belgharbi L et al. Analysis of NRA assessment data. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

²¹ Colombini A et al. Financial assessment. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

Part 2:

Objectives

Objective 1: To strengthen vaccine safety monitoring in all countries

- *As of 2009, 48% of the world population lived in countries without a functional safety monitoring system for vaccines.* ²²
- *Enhancing vaccine safety monitoring in these countries will improve their ability to reliably detect vaccine safety signals that require further action and to reduce the number of spurious signals.*
- *Several new and underutilized vaccines will be introduced in these countries in the near future.*

1.1 Rationale for action

As of 2009, 48% of the world population lived in countries without a functional safety monitoring system for vaccines.¹ The situation analysis conducted for the Blueprint shows that the surveillance of AEFI remains limited in most LMIC, although these countries utilize almost twice as many doses of vaccine as industrialized countries. Thus, few data are available on the AEFI that may have occurred in these developing countries, and fewer still on the people who may have been affected.

Most vaccine products used in LMIC differ from those available in industrialized countries (e.g. OPV instead of IPV, combination products with DTwP instead of DTaP, plus very often the products involve different manufacturers),²³ so assumptions about vaccine safety are not necessarily transferable. However, with progress made in the control of vaccine-preventable diseases, attention to AEFI has increased in LMIC, just as it did in high-income countries in past decades.²⁴ Public concerns about vaccine safety affect all immunization programmes. In countries with weak vaccine safety monitoring systems and limited ability to address safety signals, such alerts have resulted in unnecessary disruptions of vaccination programmes. Although it is not sufficient by itself, the simplest component of a vaccine safety monitoring system is the process for spontaneous reporting of any AEFI (also referred to as passive surveillance), by health-care workers or members of the community.

²² Belgharbi L et al. Analysis of NRA assessment data. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

²³ Milstien JB, Kaddar M. The role of emerging manufacturers in access to innovative vaccines of public health importance. *Vaccine*, 2010, 28:2115–2121.

²⁴ Chen RT et al. Challenges and controversies in immunization safety. *Infectious Disease Clinics of North America*. 2001, 15:21–39.

A structured approach for spontaneous reporting of AEFI is a basic element of vaccine safety monitoring. Putting AEFI information into perspective requires the additional ability to interpret and analyse available data. For national authorities to use that information fully, there is a need for standard definitions and reporting formats that enhance the ability to exchange and compare information, to verify vaccine safety signals and other safety issues, as well as to evaluate trends. Efforts are required to improve data-sharing and interactions between immunization programmes and NRAs, in order to make AEFI data available to the regulators and to the corresponding vaccine manufacturer. In several countries, signal detection has moved beyond passive reporting and monitoring of AEFI, to stimulated reporting for specified outcomes and, ultimately, to using cohorts of individuals in which outcome and vaccine exposure information is captured.

LMIC that introduce new vaccines often have limited ability to monitor the occurrence of conditions of particular interest that could be related to vaccine use. However, existing epidemiological networks in many of these countries could be adapted to monitor vaccine safety, especially in the context of a new vaccine introduction. Nevertheless, in the context of mass vaccination campaigns against meningococcus A (MenAfriVac) in West African countries during 2010, it has been possible for enhanced spontaneous reporting, prompt investigation of serious AEFI and limited active surveillance to be carried out by teams of specially trained local investigators.²⁵ This has demonstrated that it is possible to evaluate the safety of a new vaccine in populations where safety surveillance for routine vaccinations has, so far, been limited.

1.2 Targets and outputs

Target 1: Effective spontaneous reporting of AEFI in all countries

AEFI reports:

Improved implementation of spontaneous AEFI reporting and global pooling of AEFI data allows all countries to reduce the time necessary for identifying rare vaccine reactions, and to compare the local safety profile of a specific product with that observed in other countries. In order that the safety profile of newly-available vaccines is adequately monitored beyond the stages of clinical development, it is proposed that countries introducing newly-available vaccines, and countries where prequalified vaccines are manufactured and utilized, should have the capacity to implement active AEFI surveillance for those products. It will be critical to establish standard methodologies for active surveillance (particularly ongoing surveillance systems for selected conditions of interest) in countries with advanced vaccine safety systems, and also ad hoc surveillance, to evaluate the introduction of a specific vaccine, in countries that meet only minimal capacity levels.

²⁵ Global Advisory Committee on Vaccine Safety. Meeting of the Global Advisory Committee on Vaccine Safety, June 2011. Weekly epidemiological record, 2011, 30:321–324.

Outputs:

Procedures for detecting and reporting AEFI will be in place at country level, as well as sufficient numbers of trained staff. Data will be regularly analysed and communicated, at least annually, to international level. Also at international level, a global repository is needed for the storage of national spontaneous AEFI reports. The WHO Collaborating Centre for International Drug Monitoring currently provides this function for pharmacovigilance. A standard reporting format for AEFI should be developed and validated, together with a manual for its use. Spontaneous reporting of AEFI will be facilitated by the proposed standard format that will identify core variables for vaccine safety monitoring to each country. This will assist health professionals and others, who report AEFI, to provide consistent information on all cases so that data can be compared and patterns of potential safety signals can be identified. Data will also be compared internationally.

In order to achieve this outcome and maintain consistency in reporting, activities will include the development of international standard operating procedures for spontaneous reporting of AEFI, and the institution of periodic analyses and reports of spontaneous AEFI surveillance at both country and intercountry levels. Benchmarks for evaluation of AEFI surveillance (performance indicators) will be agreed, and there will be regular evaluation of AEFI surveillance against these benchmarks. There will also need to be continuing work on methodologies for signal detection in surveillance databases.

A qualified national AEFI expert review committee (ARC) is essential for guiding signal verification and issuing recommendations regarding the actions to be considered by the competent national authorities: communication only; further investigation, or direct action for prevention or control. A well-constituted and experienced ARC, with clear workflows and routes of communication, is needed at this crucial stage. In addition to providing technical advice, national expert committees offer the potential to advise national authorities on the monitoring and evaluation of their development plans for evaluating vaccine safety. Such a mechanism should be in place in regions where new vaccines are introduced, or in countries that manufacture vaccines. For adjacent countries and groups of small island states, an intercountry AEFI committee could potentially be set up for this purpose. International guidance on ARCs exists, but will need to be expanded to take into account lessons learned from countries that have implemented these expert committees over several years. ARCs with a higher level of expertise will be necessary in countries that undertake their own epidemiological investigations.

Through a WHO-led pilot project, 12 countries are currently collaborating in an attempt to pool their vaccine safety data in a single global database. This effort will lead to a recommended standard format for exchanging AEFI information. It will serve as a demonstration of the value of global exchange of vaccine safety information for signal detection, with an initial focus on WHO prequalified vaccines. As a database repository, it is also expected to encourage important secondary analyses of AEFI, following the collation of data over time. Subsequently, it is envisioned that the models developed with these 12 countries could be adopted by others in their respective geographic areas, and that local expertise in participating in the global collaboration will provide an additional decentralized resource for regional technical support.

Target 2: *Enhanced capacity for vaccine pharmacovigilance in countries that manufacture vaccines and countries where newly available vaccines are being introduced*

Enhanced capacity for monitoring vaccine reactions

Enhanced capacity means the ability to reliably identify the signals that require further action. Countries should have the ability:

- to establish background rates for events of interest;
- to reliably detect potential adverse events in the vaccinated population;
- to validate cases and confirm the vaccine exposure.

In order to protect the safety of their populations, all countries that introduce newly-available vaccines should be in a position to conduct prospective monitoring for potential AEFI of interest. This is currently the case for rotavirus vaccines and the risks of intussusception, following the model developed by the WHO Region of the Americas and based on WHO's manual for the post-marketing surveillance of rotavirus vaccine safety.^{26, 27} Advanced planning is essential so that well-functioning systems are in place before new vaccines are introduced. Much of this work is expected to involve searching relevant health databases and sets of medical records. A global platform will help coordinate active surveillance activities and will assist in the analysis of data from different locations. Several technical partners and regulatory authorities have experience that will provide the basis for a global support network. Although much of the effort so far has been targeted to newly-available vaccines, there is also a need to monitor the safety of those older vaccines now being produced by a new manufacturer.

Outputs:

Countries where newly-available vaccines are being introduced, and those that manufacture and use prequalified vaccines, will require levels of vaccine pharmacovigilance beyond passive surveillance. In these cases, agreed methods of active surveillance, such as stimulated reporting and cohort studies, should be used. International guidance will be developed on active surveillance for AEFI — i.e. harmonized tools and technologies for actively seeking out signs of specific conditions following vaccination, proposed benchmarks for implementing active surveillance and recommended analytical methods. These countries will have the ability, at national level, to conduct advanced epidemiological studies that control for important covariates. Background rates (i.e. the rates of prevalence of the conditions of interest in the unvaccinated population) should be characterized in advance of vaccine introduction, and computerized clinical databases and other technologies should be used wherever possible.

²⁶ Safety of rotavirus vaccines: postmarketing surveillance in the WHO Region of the Americas. Weekly epidemiological record, 2011, 86(8):61–72 (<http://www.who.int/wer/2011/wer8608/en/index.html>).

²⁷ Post-marketing surveillance of rotavirus vaccine safety. Geneva, World Health Organization, 2009 (WHO/IVB/09-01).

National resources and facilities need to be created or strengthened for carrying out active surveillance. Methodologies and procedures will be developed for active surveillance, as well as implementation plans. These methodologies will then be piloted by countries that participate in the Global Vaccine Safety Initiative, in particular when introducing newly-available vaccines. These countries are expected to demonstrate active surveillance reporting systems that have increased capacity, satisfactory sensitivity and assessment of lack of bias. Similarly, as countries' ability to conduct cohort studies is enhanced, more countries will be able to conduct these studies with limited controlling for covariates. To ensure appropriate implementation, performance indicators will be developed to evaluate enhanced systems of vaccine safety monitoring.

The tools outlined under this objective are just a few of those that will be developed within the Blueprint project. While many tools will be computer-based, this will not always be the case. Reporting forms may need to continue to be on paper, especially in settings where computer technology cannot easily be sustained or where there are few people skilled in its use. In many cases, the tools already exist but require adaptation, including translation, before they can be piloted and eventually put to general use. Objective 4 focuses specifically on the development of harmonized tools and methods to support the expansion of vaccine safety activities.

Objective 2: To strengthen the ability of countries to evaluate vaccine safety signals

- *Vaccine safety signals must be validated properly so that appropriate public-health decisions on vaccine use can be made.*
- *Most countries do not have the ability to conduct epidemiological risk assessment of vaccine safety signals, despite the importance of this for public safety.*
- *Absence, or deficiency of such capacity, has jeopardized immunization programmes in the past.*

2.1 Rationale for action

Monitoring of vaccines after their use, as outlined in Objective 1, may detect a potential safety issue or signal. Effective evaluation and response are crucial, as such signals may rapidly become a threat to health if they are not promptly investigated.^{28, 29, 30} For the safety of vaccinees, it is important for countries to confirm a signal as a potential public-health issue, or dismiss a spurious association which might otherwise damage an effective vaccination programme. The capacity to evaluate and respond to vaccine safety signals is particularly important for countries with newly-introduced vaccines.

The first step of signal evaluation is to verify the source, validity and type of the signal, in order to initiate and select the most adequate public-health response strategy. This is critical for planning concerted action and clear communication to professionals and the public alike. If the initial verification process validates or strengthens the signal, a second step is needed, namely to determine whether the observed AEFI is *associated with* the alleged vaccine and, if so, to determine the causal relationship and quantify the public-health risk. The detection and validation of the signal can be performed through a review of cases identified by reporting systems, but the assessment of associations, causal relationships and public-health risk requires, among other things, well-controlled epidemiological studies and assessment of background rates of events³¹, including the use of appropriate denominators. This, in turn, implies unbiased case ascertainment that can be greatly facilitated by databases or registries of immunization and health outcomes.

²⁸ Wharton M. Vaccine safety: current systems and recent findings. *Current Opinion in Pediatrics*, 2010, 22(1):88–93.

²⁹ Chen RT et al. Vaccine Safety Datalink Project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics*, 1997, 99:765–773.

³⁰ Duclos P. A global perspective on vaccine safety. *Vaccine*, 2004, 22:2059–2063.

³¹ Siegrist CA et al. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be. *Pediatric Infectious Disease Journal*, 2007, 26:979–984.

There is a need for national systems that can evaluate signals from different sources and take the appropriate action rapidly. The evaluation of data requires specialized knowledge and skills that may not be available in all countries, especially if surveillance has not been routinely carried out in the past.³² Capacity-building will be important for strengthening countries' ability to evaluate the results of monitoring, as discussed in Objective 6. With local capacity to verify vaccine safety signals, the speed of identification and analysis will be increased, and the delay in action to protect public health and to communicate scientifically-accurate information will be minimized. National ARC will play an important role in providing expert advice on safety signals, and will also serve as a link to international advice and training, as outlined in Objective 7.

If a vaccine safety issue is identified and validated in a given country, it is important that this information is communicated to other countries using the same vaccine (so that action can be taken, if appropriate, to protect the health of vaccinees worldwide) and to the vaccine manufacturers (so that further analysis and the necessary corrective action can be taken). Objective 8 describes the need to establish mechanisms for cooperation and information-sharing between NRAs, international agencies and manufacturers.

2.2 Targets and outputs

Target 1: *Countries, alone and/or in collaboration with others, have the ability to verify vaccine safety signals and initiate appropriate public-health actions.*

Outputs:

Countries will have developed appropriate national capacity to review the evidence behind a signal, to determine the source, nature and type of the signal, and to determine the adequate response strategy depending on source, nature and type of signal. Tangible products will include: an updated manual for the establishment of an ARC or a technical review committee; standard operating procedures to determine the source, nature and type of signal; a platform for information exchange and knowledge transfer between countries; tools and strategies for systematic follow-up to substantiate signals; guidance and shared protocols for case definitions and the conduct of comparative studies, as well as training modules to build capacity for signal strengthening.

³² Yih WK et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink Project. *Pediatrics*, 2011, 127(Suppl. 1):S54–S64.

Target 2: *Countries have the ability to investigate a potential public-health risk*

Outputs:

In selected countries, access to health-care data sources for investigation will enable epidemiological studies assessing causal association (alone, or in collaboration with others), to be carried out. The current lack of such capacity in all countries dictates that collaboration takes place whenever possible and when consultative resources are available. This includes the technical and investigational capacity to share and communicate data among stakeholders. Tangible products will include guides to establish and utilize immunization data sources, to establish, standardize and utilize health-outcome data sources, and to link immunization and outcome information. There will also be training modules for: building analytical capacity for epidemiological studies; technical infrastructures and methodologies for the collection, elaboration and analysis of data; a guide for communication of findings between investigators, public-health agencies (PHAs) and NRAs, and an inventory of supportive legal support frameworks for data access and sharing. National, regional and global expertise will be made available to assist in this effort and support capacity building.

Target 3: *Countries have the ability to interact internationally for signal evaluation and internationally concerted public-health action*

Outputs:

Given the amount of work required to investigate a vaccine safety signal, and the implications of such investigations for other countries, international collaboration should be facilitated. The achievement of this target will require appropriate national capacity to participate in international data sharing, to take part in internationally concerted public-health action, and to have defined access to trained personnel who are qualified to verify vaccine safety signals. Tangible products will include: template workflows for data sharing between stakeholders at national level; instructions for use of international data-sharing infrastructures; technical platforms for local data entry, elaboration and transfer; shared protocols for controlled epidemiological and mechanistic studies, and training modules for building local analytical capacity.

Objective 3: To develop vaccine safety communication plans at country level, to promote awareness of vaccine risks and benefits, understand perceptions of risk and prepare for managing any adverse events and concerns about vaccine safety promptly

- *Communication about vaccine safety is more than crisis management.*
- *There is a need for education of the population on the balance of risk and benefit in vaccination.*
- *Appropriate skills and training are required to communicate the element of uncertainty.*

3.1 Rationale for action

Communication is more than just telling people what they ought — and have a right — to know, and it is more than just making information available promptly so that people can make informed decisions. Communication is also about listening to what people say in order to better understand their needs, concerns and priorities.

Communication with local communities, health-care workers and decision-makers

Communication of open, evidence-based information about the importance of vaccination and the safety of specific vaccines to the public, as well as to health-care providers and decision-makers, is crucial for public confidence.³³ Decision-makers, who authorize the use of vaccines, and health-care workers, who administer them, need to be fully aware of the many benefits, as well as any potential risks, of each specific vaccine, and should be able to communicate these benefits and risks as well as the rationale for vaccine-related policies. Any evidence that a vaccine might cause harm must be taken seriously and communicated promptly, and appropriately, to the regulators, to health workers and to communities, who have a right to know about any potential vaccine risks, no matter how small they may be.

Each country should have a communication strategy that includes ongoing communication (including educational programmes for children and parents) on the benefits and risks of specific vaccines, as well as relevant information on their storage and administration. Specific communication strategies should be tailored to the needs of decision-makers, professional and scientific associations, health-care workers, the media and the public. In addition, crisis-management plans should be in place to respond promptly to AEFI and outbreaks of public distrust due to AEFI, or new information (or misinformation) on vaccines.

National pharmacovigilance centres, in collaboration with immunization programmes and NRAs, should maintain information about the safety profile of vaccines used locally. This information should be based on locally-generated data, as well as on global reference materials on vaccine safety. Information on vaccine safety should be publicly accessible, and should be communicated to all persons concerned with the use of each respective vaccine.

³³ Larson HJ et al. Addressing the vaccine confidence gap. *The Lancet*, 2011 (Early online publication 9 June 2011. doi:10.1016/S0140-6736(11)60678-8).

Similarly, at global level, information on vaccine safety issues of local or global importance should be communicated to all persons concerned with the use of the particular vaccine(s). Messages should be adapted to the information needs of at least three important groups — communities, health-care workers and decision-makers — and should be translated into the relevant local languages. The Vaccine Safety Net provides a validated list of web sites that adhere to good information practices on vaccine safety. Those sites have been assessed in terms of credibility, content, accessibility and design.³⁴

Management of persistent public concerns and vaccine safety rumours

All countries need to develop locally-relevant communication strategies for rapid response to public concerns, including those relating to AEFI. Whether a public concern reveals an underlying problem, or is shown to be unfounded, if the concern persists it should be addressed through dialogue with the communities concerned. Rumours about the safety of vaccines can also develop into major challenges. Systems will be designed to respond quickly, in order to pre-empt a drop in public confidence in vaccination, and also possible disruptions to immunization programmes when such rumours are identified.

3.2 Targets and outputs

Target 1: *To develop or strengthen the ability of countries to support ongoing communication between local communities, health-care workers and decision-makers about important vaccine safety issues (local or international) that include risk preparedness*

Outputs:

Activities undertaken to reach this target are expected to result in ongoing communication between local communities, health-care workers and decision-makers about vaccine safety issues (local or international) that include risk preparedness. The best communication guidance will be made available, and there will be global assessment of existing vaccine communication at country, regional and international levels, in order to support countries in efforts to develop capacity for vaccine safety communication.

National communication strategies will include ongoing risk–benefit communication on vaccine safety, both for the general population and for specific target groups. This will include focus on the balance of risk and benefit, the benefits of vaccination to the individual and society and the importance of reporting any AEFI that are observed. Messages and other communication tools addressing vaccine safety concerns will be developed and made available, in order to present in clear and balanced terms the nature of the issues, possible risks that are being addressed and the steps taken in response to alerts. Media training will help community leaders to give clear, factual and consistent messages to the media, and media workshops will help journalists understand the key issues in vaccine safety.

³⁴ World Health Organization. Vaccine safety net (http://www.who.int/immunization_safety/safety_quality/vaccine_safety_websites/en/).

Target 2: *Vaccine safety concerns of local and global significance will be investigated promptly and communications strategies put in place; in some cases, even if a concern is discovered to be unfounded, communication strategies will be needed to manage persisting public concerns*

Outputs:

Activities undertaken to reach this target should lead to the investigation of vaccine safety concerns of local and global significance, and prompt responses to understand and address public concerns which arise due to new vaccine information, or AEFI. The focus will be on explaining the nature of real problems and what is done to minimize them. With respect to unfounded allegations, the focus will be on maintaining public confidence in the effectiveness of vaccines, and allaying fears of unacceptable risk, so that people will continue to protect their health, and the health of their children, through vaccination. Activities will be supported by information surveillance systems to detect early signals of public concern, strengthened capacity of countries and relevant international bodies to respond to public concerns and guidance from the Vaccine Safety Net on credible web-based vaccine safety information.

Objective 4: To develop internationally harmonized tools and methods to support country vaccine safety activities

- *Different countries have different needs in developing their vaccine safety systems.*
- *New technologies are available to manage information.*
- *International standardization of data records will facilitate information exchange and the global identification of vaccine safety signals.*

4.1. Rationale for action

Following immunization, the safety of a vaccine is assessed by the absence of an increased risk of AEFI in the vaccinees. Because serious vaccine-attributable conditions are rare, clinical studies that are limited to several thousand subjects (and occasionally tens of thousands) often yield insufficient safety data. Therefore, clinical development studies are not sufficiently powerful to rule out the possibility that a small risk may exist. In addition, most vaccines are licensed before data are available about their use in several important population groups — such as, pregnant women, people with chronic conditions or people with a possible specific genetic predisposition. However, by aggregating the findings from multiple studies, vaccine safety profiles may be seen to include several rare conditions that were unidentified in the past, and the possibility of others may be refuted on the basis of available evidence.

Combining data from multiple studies can be effective only if these studies are based on similar definitions of the AEFI they have investigated, which is often not the case. While varied tools and methodologies are available in different countries, there are no global standards, and many countries have gaps in their vaccine safety systems. Unless similar outcomes are being measured with comparable methodologies, there is uncertainty as to what the investigations have really shown, and this complicates the compilation of reliable global statistics on vaccine safety. Countries already have a range of different resources with variation in capacities to arrive at clinical diagnoses, and they will also have different needs in implementing this and other objectives.

With standardized case definitions in place and comparable data in them, databases at global level can be used, not simply for collating and searching data, but for testing hypotheses about possible vaccine-attributable conditions.³⁵ In the past 10 years, the Brighton Collaboration has developed over 20 case definitions that have been applied to the monitoring of vaccine reactions in clinical trials, and after the vaccines have been licensed for large-scale use.^{36, 37} Some of these case definitions will need to be field-tested to evaluate their suitability for use in clinical and research practice in LMIC.

As a result of such work, problems will not only be detected with greater certainty, but the accuracy of the data will enable unfounded allegations and misleading information about vaccines to be countered with greater confidence, as provided for in Objective 3.

³⁵ Black S. Global Vaccine Safety Datanet meeting. Expert Review of Vaccines, 2008, 7:15–20.

³⁶ Kohl KS et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. Pharmacoepidemiology and Drug Safety, 2003, 12:335–340.

³⁷ Kohl KS et al. The development of standardized case definitions and guidelines for adverse events following immunization. Vaccine, 2007, 25:5671–5674.

4.2. Targets and outputs

Target 1: *Standard procedures and methodologies will be available for identification of vaccine safety signals*

Outputs:

Standardized reporting will assist health professionals and others who report AEFI to provide consistent information on all cases so that data can be compared and patterns of potential safety signals can be identified at national and global levels.³⁸ Existing case definitions will be field-tested to evaluate their suitability for use in clinical and research practice in LMIC. To reflect the needs of LMIC, existing case definitions may be revised to make them more appropriate to local situations, and new case definitions will be developed. Translations will also be required to make the standard format, procedures and case definitions suitable for use in the settings targeted by the Blueprint initiative.

A set of standardized tools and methods that can be used globally for the identification and assessment of a given AEFI will enable vaccine safety data collected from a range of sources (clinical trials, post-marketing surveillance, individual case reports and retrospective epidemiological studies), in a range of locations, to be collated and compared in order to give more accurate numbers of specific AEFI and a more realistic picture of vaccine safety.³⁹ Global guidance documents, for the investigation and classification of AEFI of interest, will need to be updated and made available in several languages.

Target 2: *Standard procedures and methodologies will be available for analysing and investigating vaccine safety signals*

Outputs:

Specific products will include updated global guidance documents for the investigation and classification of AEFI of interest. These documents will be made available in relevant languages. International guidance on active surveillance for AEFI, including stimulated surveillance and signal identification through cohort studies, will be developed, including harmonized tools and technologies for actively seeking out signs of specific conditions following vaccination, proposed benchmarks for implementing such surveillance and recommended analytical methods.

³⁸ The Brighton Collaboration. Case definitions and guidelines (<http://brightoncollaboration.org>). Uppsala Monitoring Centre (<http://www.who-umc.org/>).

³⁹ Bonhoeffer J et al. Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. *Vaccine*, 2009, 27:2289–2297.

Target 3: *Various tools will be available to facilitate vaccine pharmacovigilance*

Outputs:

Specific products will include a global vaccine product dictionary which will be developed and made available by the WHO Global Programme for International Drug Monitoring (Uppsala Monitoring Centre). A standard format will also be defined for the exchange of information from medical records. Computerized medical record data will become accessible for vaccine safety studies through a global network of facilities, allowing pooling of data and testing of hypotheses. Vaccine product identification and lot numbers also provide important information with regard to vaccine safety issues. Given the difficulties encountered in collecting such information, special efforts will be made to advocate for global adoption of appropriate systems aimed at ensuring the traceability of individual vaccine products (e.g. barcodes, radio frequency identification, or other means).

Objective 5: To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels

- *An effective vaccine safety system cannot be maintained without strong regulatory support.*
- *Collaboration between immunization programmes and national regulatory authorities is key to ensuring that vaccines are monitored for safety even after licensing.*
- *Clear requirements, clear responsibilities and enforcement of regulations help protect health.*

5.1 Rationale for action

The effectiveness of vaccine pharmacovigilance, as for all medicinal products, should be enforced by a regulatory system backed up by the appropriate laws, regulations and procedures. Proper implementation depends on a system that is coordinated and managed by a functional administrative mechanism with a clear mandate.

NRAs are responsible for ensuring the safety of medicines and vaccines within their country — such as by overseeing the conduct of clinical trials, monitoring the safety of medicines and vaccines and ensuring communication between all the parties concerned. Several countries also have designated pharmacovigilance centres that typically carry out post-marketing surveillance of medicines. When countries use vaccines, there should be an obligation to have a functioning vaccine pharmacovigilance system in place that has attained a given standard.

Immunization programmes and health-care workers play a major part in detecting and reporting AEFI. Systems also have to be in place to assess the cause of serious AEFI, should they occur, in order to maintain public confidence. Should an event be causally related to a vaccine, NRAs must have the authority to take action and to provide feedback to the programme and other key institutions, to enable prompt public and political decision-making. They should also have the authority to demand safety studies, including active monitoring, from manufacturers and/or importers of vaccines.

Functional vaccine pharmacovigilance with lines of accountability

In many countries, vaccine pharmacovigilance systems are supported by regulatory provisions with clearly defined lines of accountability. Many other countries, however, do not have such provisions, or their vaccine pharmacovigilance system is not fully functional. National vaccine pharmacovigilance centres will need to be established in all countries and existing centres will need to be strengthened. The possibility that groups of small countries, using the same vaccine product, may collaborate to pool their AEFI data is another option to be considered. The intention is to encourage and assist each country in establishing a set of official requirements for vaccine pharmacovigilance systems that would allow timely identification of the most common vaccine safety problems.

Vaccine pharmacovigilance as an international responsibility

Few vaccines are specific to one country. As vaccines are used internationally, vaccine safety data from one country are also of importance to others. Vaccine safety is both a national and an international responsibility. As countries develop their legal and administrative structures, to improve their vaccine pharmacovigilance, and as worldwide AEFI data are pooled and analysed in global databases, the information generated should be shared with decision-makers at both national and international levels.

International Health Regulations

The International Health Regulations (IHR) 2005⁴⁰ came into force on 15 June 2007, requiring 194 countries (States Parties) to adhere to the regulations. The IHR aim to assess the ability of national structures and resources to meet minimum national core capacities for surveillance and response to disease outbreaks, as well as other events that may constitute a “public-health emergency of international concern.” Such events may include AEFI caused by a vaccine introduced in several countries. Each State Party is also required to develop a plan of action so that the core capacities are present and functioning throughout its respective territory by 2012.

5.2 Targets and outputs

Target 1: All countries have provisions for establishing vaccine pharmacovigilance, including lines of accountability

Outputs:

Activities undertaken to reach this target are expected to lead to a more formalized system of vaccine pharmacovigilance, with official requirements for lines of accountability and publicly available official regulations that prescribe vaccine safety activities. There should also be a quality management system for these activities. In addition, there will be functioning national pharmacovigilance centres and national expert committees for vaccine safety that maintain safety profiles for vaccines used in immunization programmes. In several countries, vaccine pharmacovigilance centres will have to form a collaborative link between the national drug regulatory authority and the national expanded programme on immunization. Clear guidelines should be provided on how these two organizations can collaborate in vaccine pharmacovigilance.

The roles and responsibilities of marketing authorization holders and of national authorities in conducting vaccine pharmacovigilance will be specified in detail. A routine and functioning system for regular review of the safety and impact of specific vaccines should include a process for reviewing and sharing data, both with national, and international stakeholders (see Objective 8). In addition, pharmacovigilance reports will be generated periodically and will be communicated through WHO regional offices.

⁴⁰ International Health Regulations (2005). Geneva, World Health Organization, 2005 (<http://www.who.int/ihr/en/>).

Target 2: Vaccine pharmacovigilance is established as an international responsibility

Outputs:

An international mechanism will be established for the exchange of information about AEFI and vaccine safety. As WHO manages the United Nations vaccines prequalification programme, it is intended that the safety profile of all prequalified vaccines be validated by the Global Advisory Committee on Vaccine Safety. For the sake of transparency, the rates of observed vaccine reactions for prequalified vaccines will be published on the WHO web site.

Objective 6: To strengthen regional and global technical support platforms that meet countries' expressed needs

- *To build capacity for national vaccine pharmacovigilance, substantial training is needed.*
- *Technical expertise should be available to all countries to address vaccine safety issues.*
- *Multicountry studies will help clarify complex vaccine safety issues.*

6.1 Rationale for action

The situation assessment carried out for the Blueprint initiative, together with reports from WHO regional offices, confirmed that countries urgently need effective systems of pharmacovigilance to monitor the safety of medicines and vaccines.^{41,42} Expert advice and guidance is available internationally from many organizations (national or international technical agencies, academia, national experts from immunization programmes, pharmacovigilance centres or regulatory agencies), but will need to be tailored to the specific needs of each country according to the level of development of the national regulatory system, including institutions such as the NRA, pharmacovigilance centres, national control laboratories and the immunization programmes. Advice, guidance and technical support should aim to strengthen existing functioning infrastructure and to build on it in a stepwise process.

The WHO process for strengthening national regulatory systems through the use of an institutional development plan that addresses gaps and weaknesses involves a variety of institutions and organizations worldwide.⁴³ This initiative can provide a cornerstone of the effort to provide assistance and training for building local capacity in vaccine pharmacovigilance.

Access to training resources

In collaboration with all institutions that contribute to the international support structure, a global resource will be assembled that provides training materials and a pool of qualified trainers from accredited training institutions at global, regional and subregional levels. Training curricula on general principles of vaccine safety, as well as advanced methods of vaccine pharmacovigilance, will be available to countries. The network of trainers to be assembled will be available to respond to national training needs with appropriate cultural and language skills, while referring to commonly developed training objectives.

⁴¹ Li Y et al. The capacity and needs of post-marketing vaccine safety monitoring in low- and middle-income countries. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

⁴² Belgharbi L et al. Analysis of NRA assessment data. In: Global vaccine safety blueprint — the landscape analysis. Geneva, World Health Organization (WHO/IVB/12.04).

⁴³ World Health Organization (2003). Aide memoire. Strengthening national regulatory authorities (<http://whqlibdoc.who.int/hq/2003/a80815.pdf>).

Technical support to respond to specific vaccine safety issues

The validation and investigation of vaccine safety signals have been discussed under Objective 2. Even when countries have established minimal capacity for vaccine safety, a situation may arise in which external technical support is required. This may be in the form of access to specialized laboratory procedures or to technical expertise in specialized epidemiological studies. Here, also, a global pool of experienced vaccine pharmacovigilance experts, and a network of support institutions, will provide decentralized support with easier geographical access and language compatibility. This network will also be a useful resource for advice on communication and response to vaccine safety crises.

Global and regional infrastructure to coordinate multicountry studies on vaccine safety

Many vaccine safety issues are too rare, or require such overly specialized diagnostic capacity that it would not be practical, or even possible, for most countries to conduct adequate studies to clarify the issue alone. To meet the need for coordinated global and regional infrastructure, the Blueprint collaborative mechanism, a network of institutions that meet a certified level of clinical practice and that have expressed interest in multicountry vaccine pharmacovigilance studies, will be developed from institutions that agree with jointly developed procedures for such studies. Study proposals could subsequently be submitted through a network secretariat that would facilitate the review and implementation of these projects.

6.2 Targets and outputs

Target 1: A strengthened global or regional mechanism that facilitates access to learning/training for the development of national vaccine pharmacovigilance capacity

Outputs:

Training curricula for vaccine safety will be developed and regularly updated to meet the needs of all levels of the health-care system and to integrate new developments in the field of vaccine safety. Country capacity in AEFI evaluation and investigation will be strengthened through training activities for national personnel. The focus of training will vary from country-to-country according to local needs, as determined through an assessment measured against WHO-proposed indicators. Among other aspects, training would offer an overview of the safety profile of vaccines used locally, an understanding of existing national systems, a description of the conduct of a case investigation, the basic principles for assessing causality and risk–benefit analyses and an approach to the critical evaluation of vaccine safety literature.

Target 2: *A global or regional mechanism that provides technical support to respond to specific vaccine safety issues*

Outputs:

Expert support will be facilitated by an international support structure and will be provided to countries through a decentralized network of institutions and organizations that will include adequate language capacity to provide assistance to all countries. Activities designed to reach this target will include those to strengthen and maintain a pool of experts and institutions with expertise in vaccine pharmacovigilance. A mechanism will be developed to ensure that international vaccine safety expertise is available to the required standard. WHO has a role to play as an unbiased technical arbiter and also as the coordinator of crisis assistance.

Activities will include developing and maintaining an inventory of best practices for vaccine pharmacovigilance and evaluation, and setting up a global health-care data network, through which international researchers will be able to test hypotheses related to the safety of vaccines. Epidemiological studies, for use at national and multicountry levels, will also be developed to assess important safety signals.

Target 3: *Identification and strengthening of a global and regional infrastructure that coordinates multicountry studies related to vaccine safety issues*

Outputs:

Activities undertaken to reach this target are expected to lead to a global or regional infrastructure that facilitates the procedures for multicountry collaborative studies addressing vaccine safety issues. In particular, this will require the establishment and maintenance of an inventory of qualified institutions to coordinate or execute such multicountry studies at global, regional and subregional levels.

Objective 7: To provide expert advice on vaccine safety issues at national, regional and international levels

- *Expert advisory groups provide important guidance for policy development on immunization programmes at national, regional and international levels.*
- *Better intelligence about the safety and efficacy of vaccines in all parts of the world, that will result from implementing the Blueprint, will provide these advisory groups with a stronger evidence base.*
- *GACVS will act as the scientific advisory committee to the Global Vaccine Safety Initiative.*

7.1 Rationale for action

Expert advisory groups assist immunization programmes in assessing and managing the benefits and risks of vaccination. At country level, WHO promotes the establishment and regular meetings of National Immunization Technical Advisory Groups⁴⁴ as well as AEFI review committees (ARC). In addition, all WHO regions have their own technical advisory group to provide policy guidance. At global level, WHO currently benefits for guidance on immunization from the advice of an Expert Committee for Biological Standardization (ECBS),⁴⁵ a Strategic Advisory Group of Experts (SAGE) on Immunization,⁴⁶ an Immunization Practices Advisory Committee (IPAC)⁴⁷ and — specifically for assessing vaccine safety issues — the Global Advisory Committee on Vaccine Safety (GACVS).⁴⁸ All these committees will benefit from the products of Objectives 1–4 of the Blueprint, by accessing improved intelligence on vaccine safety issues and improved channels for disseminating their advice.

Vaccine-associated AEFI can affect healthy individuals, and should be promptly identified to allow for additional research and appropriate action. Advances in technology and increasing intelligence about the effects of vaccines have enhanced our ability to characterize rare and, even delayed reactions following vaccination. Such newly-available information on vaccine safety is critical for optimizing the safe use of vaccines. The rapid detection of vaccine safety signals of global importance should therefore be complemented by a scientifically sound assessment of the signals through studies which are analysed and evaluated by global experts.

Assistance with the evaluation of serious AEFI and potential safety signals needs to be available internationally, through access to global institutions with trained personnel who can readily provide this assistance to countries as they develop their own capabilities. International advice and assistance in evaluating and investigating AEFI should be made available to all countries and will be delivered as needed, and requested (see Objective 6). The national ARC, or other similar national structure, would be the logical link to the network of international experts on AEFI investigation.

⁴⁴ Bryson M, Duclos P, Jolly A, Cakmak N. A global look at national immunization Technical Advisory Groups. *Vaccine*, 2010; 28 (Suppl. 1):A13–A17.

⁴⁵ Expert Committee for Biological Standardization (http://www.who.int/biologicals/expert_committee/en/).

⁴⁶ Strategic Advisory Group of Experts (<http://www.who.int/immunization/sage/en/>).

⁴⁷ Immunization Practices Advisory Committee (http://www.who.int/immunization_delivery/systems_policy/ipac/en/).

⁴⁸ Global Advisory Committee on Vaccine Safety (http://www.who.int/vaccine_safety/en/).

When requested by the national ARC, a mechanism should be developed to facilitate country collaboration with international experts.

To respond promptly, efficiently and with scientific rigour, to vaccine safety issues of potential global importance, WHO established the Global Advisory Committee on Vaccine Safety (GACVS) in 1999⁴⁹. GACVS is responsible for risk assessment by considering the evidence on vaccine safety issues, and complements other bodies, such as SAGE, which deal with the mitigation of risk. GACVS discusses vaccine safety issues that are either causing public concern, or have the potential to do so. These include general safety issues that are relevant to all vaccines, some vaccine-specific concerns and safety issues related to new vaccines, or vaccines still in development. The Advisory Committee's assessments of vaccine safety are published regularly, both in print and on the WHO web site. In order that advice on key activities resulting from the implementation of the Blueprint is made available, it is intended that GACVS, as an independent body, will issue recommendations aimed at minimizing the occurrence of unwanted vaccine reactions.

7.2 Targets and outputs

At country level, the concept of minimal capacity includes the availability of an ARC. Globally, GACVS will continue to be available as the advisory body of reference for the WHO vaccine safety alert system, thereby allowing timely advice to be developed with respect to safety alerts of potential international importance. In addition, two main targets are foreseen as supporting this objective.

Target 1: *Immunization advisory bodies at national, regional and global levels provide expert advice on managing unwanted vaccine reactions*

Outputs:

Activities undertaken in reaching this target should lead expert advisory bodies to update their recommendations regularly in the light of evolving evidence regarding the safety and efficacy of specific vaccines.

Target 2: *GACVS maintains the global safety profile of all vaccines and advises on the conduct of studies for assessing vaccine safety signals of global importance*

Outputs:

Activities undertaken to reach this target should lead to a rapid and effective response to serious vaccine-related AEFI and the maintenance of confidence in vaccination activities, through regular reporting of updated vaccine safety profiles by GACVS. This is expected to lead to a harmonized analysis of vaccine safety signals of global importance, based on scientific advice on the conduct of studies, made available by GACVS.

⁴⁹ Folb PI et al. A global perspective on vaccine safety and public health: the Global Advisory Committee on Vaccine Safety. American Journal of Public Health, 2004, 94:1926–1931.

Objective 8: To put in place systems for appropriate interaction between national governments, multilateral agencies and manufacturers at national, regional and international levels

- *Vaccine manufacturers are accountable for the safety and efficacy of the products that receive marketing authorization.*
- *Safe use of vaccine can be improved with well-structured information exchange mechanisms between regulatory authorities, procurement agencies and industry.*
- *Use of harmonized tools and methods allows for more efficient exchange of information.*

8.1 Rationale for action

The importance of close collaboration between regulators and industry is well recognized in vaccine pharmacovigilance activities, and guidance has been developed, in industrialized countries, for jointly planning these activities.⁵⁰ In many LMIC, however, the ability of vaccine manufacturers to obtain information about AEFI remains limited. The survey of manufacturers conducted in preparation for the development of the Blueprint identified several important expectations regarding enhancement of the performance of both active and passive surveillance and, the development of harmonized tools and methods.⁵¹

Information on the safety of a vaccine may reach several different immunization stakeholders, including national governments (through their immunization programmes and regulatory authorities), multilateral agencies and the manufacturers. Manufacturers are responsible for vaccine quality and safety during the research, development and manufacturing phases; they are responsible for providing safe and effective products, and they are also responsible for identifying, quantifying and minimizing any health risk related to the vaccine product after it has become available on the market.

Manufacturers should regularly share the information they collect with regulators. At the same time, manufacturers expect to be kept informed of the results of vaccine pharmacovigilance and to be alerted to serious problems identified by other stakeholders. Although manufacturers have their own information networks and mechanisms for receiving vaccine safety data from nongovernment channels, these networks are not always clearly distinct from the information channels relied upon by national governments, or even by multilateral agencies. Consequently, there is potential duplication of reporting and of effort, plus uncertainty as to the roles of different stakeholders in the collection, analysis and follow-up of the information received. Furthermore, there is often concern about potential conflicts of interest when manufacturers and regulators work closely together; an issue for which clear guidelines and best-practice experiences need to be developed and shared.

⁵⁰ International Conference On Harmonization. ICH-E2E Harmonized tripartite guideline: pharmacovigilance planning. Geneva, Step 4 version cited 18 November 2004 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf).

⁵¹ II4SM. Survey of vaccine manufacturers to characterize the value and limitation of vaccine safety data available through their system, and to gather their perspective on the need for a global vaccine safety system, including their possible role in such a system, 2011.

Exchange of information is facilitated when harmonized methods and tools can be utilized. During 2005–2010 a working group on vaccine pharmacovigilance was convened by the Council for International Organizations of Medical Sciences (CIOMS), with the aim of providing global support to surveillance for vaccine safety, and of addressing the evolving need for harmonized terminology and case definitions used in vaccine pharmacovigilance. In particular, the group provided the new definition of AEFI that is used in the Blueprint, and also contributed to the development and dissemination of definitions of AEFI developed by the Brighton Collaboration.⁵² CIOMS has a long record of developing tools for pharmacovigilance, and has the capacity to involve representatives of regulatory and technical agencies, as well as industry.⁵³

8.2 Targets and outputs

Target 1: *To promote a more efficient and rapid collection and exchange of information between NRAs, multilateral agencies and vaccine manufacturers*

Outputs:

A globally harmonized mechanism should be established so that both the regulatory authorities that have provided marketing authorization for a specific vaccine, and the manufacturers of the vaccine, can more efficiently and promptly exchange relevant information on AEFI and safety signals. International guidance will be developed on the collection and exchange of AEFI. Tangible products will include an agreed set of procedures on the exchange of data on AEFI between industry and regulatory authorities, and a common global platform for the exchange to take place. Through the WHO Collaborating Centre for International Drug Monitoring, NRAs and industry can have access to individual case safety reports (ICSRs) in Vigibase. At country level, an indicator for the existence of exchange of AEFI information between regulatory authorities and manufacturers, will be added to the pharmacovigilance function of the NRAs' assessment tool.

Target 2: *Harmonized tools and methods for vaccine safety monitoring activities are agreed upon between NRAs, multilateral agencies and manufacturers*

Outputs:

International methods and tools for the monitoring and evaluation of AEFI are to be jointly reviewed and endorsed by regulatory authorities and manufacturers. Tangible products will include international reference documents for monitoring newly-available vaccines. For specific vaccines, as required, there will be product-specific guidance on the level of information that needs to be exchanged between the different stakeholders, as well as on the timelines for this exchange.

⁵² Definition and application of terms for vaccine pharmacovigilance. Report of a CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva, Council for International Organizations of Medical Sciences, 2012 (ISBN 978 92 9036 083 4).

⁵³ Current challenges in pharmacovigilance: pragmatic approaches. Report of CIOMS Working Group V. Geneva, Council for International Organizations of Medical Sciences, 2001 (ISBN 92 9036 074).

Part 3:

Framework for implementation

Implementation of the Global Vaccine Safety Blueprint

Introduction

All countries should regularly assess the performance of their vaccine safety systems and prepare development plans to close any gaps that are identified. The Global Vaccine Safety Blueprint is a global strategy that has been designed as a framework for the collaboration of multiple stakeholders, under the umbrella of WHO, in supporting LMIC to strengthen their capacity for vaccine safety activities. A number of agencies, institutions and other groups (including the private sector) have been interested and active in the area of vaccine safety in LMIC for some time, but there has been little or no coordination of their efforts. Many of them have contributed to the development of the Blueprint through a Collaborative Group (which regularly advised the project Secretariat), through a Consultative Committee (which reviewed the development and reports of the situation analysis studies and subsequently reviewed drafts of the Blueprint), or as participants in briefings offered by the Secretariat throughout the course of the Blueprint development process. The Global Vaccine Safety Initiative is the proposed mechanism for implementing the Blueprint strategies.

Function and institutional base

Implementation of the Blueprint strategy will focus on the coordination of support to countries in building and strengthening capacity for vaccine pharmacovigilance, enhancing this capacity in countries that introduce newly-available vaccines, fostering international collaboration and encouraging strategic planning, so that all new vaccines are under adequate surveillance, and safety information is shared internationally. Through such implementation activities and long-term collaborative relationships, the Blueprint will contribute to capacity-building for national regulation of vaccines and drugs, laboratory investigative capabilities and health-system management.

Specific activities will be outlined in a work plan. Depending on resources that are initially available, the roll-out of activities will require a phased approach which will require a management process for decision-making.

The Blueprint implementation process will bring together the following:

- intergovernmental organizations, including WHO, and international nongovernmental bodies with an active involvement in the area of vaccine pharmacovigilance;
- government institutions and agencies involved in regulatory activities relating to vaccine pharmacovigilance;
- international industry associations/umbrella organizations that have demonstrated interest and experience in the area of vaccine pharmacovigilance;
- WHO collaborating centres that are active in the field of pharmacovigilance and vaccine pharmacovigilance;
- academic and research institutions involved in pharmacovigilance, vaccine pharmacovigilance, epidemiology, statistics and communication.

Terms of Reference have been drafted for the process of coordinating the implementation of activities by collaborating parties. The Global Vaccine Safety Initiative will be facilitated by WHO, which will provide the Secretariat, and collaborating partners will meet as a forum and operate by consensus. The initiative will not be a legal entity but will constitute a reference for guidelines, policies and actions relating to Blueprint implementation under the responsibility, and according to the mandate, of each participating organization, agency or institution.

Global Vaccine Safety Initiative — a minimal structure

The focus of the Global Vaccine Safety Blueprint is on operation rather than organizational structure. Consequently, implemented at both national and international levels by the collaborating parties and coordinated by WHO, the initiative will be guided by an annual General Meeting consisting of representatives of all participating organizations, agencies and institutions. Observers may be invited to the General Meeting and to other meetings of the Initiative. In order to coordinate the work of the General Meeting and to ensure that the implementation takes place as planned, the General Meeting will appoint a Planning Group from among its members. Among its other tasks, the Planning Group will identify the need for, and composition of, participant Working Groups to work on specific issues relevant to implementing the Blueprint.

In addition to providing the Secretariat for the initiative, WHO will also act as a central repository of information and documentation relating to implementation of the Blueprint. In addition, WHO will establish and maintain a Global Vaccine Safety Blueprint internet web site.

As a part of its current functions, GACVS will act as the scientific advisory committee to the Global Vaccine Safety Blueprint implementation.

Workplan

A generic work plan was designed, as the Blueprint was being developed, in order to illustrate the components needed and actions required for the implementation of the Blueprint goals and objectives, with the primary focus on supporting countries that express interest in establishing minimal or enhanced capacity for vaccine pharmacovigilance. The work plan identifies priorities, estimates resource needs and proposes roles and responsibilities in implementing the Blueprint during the Decade of Vaccines. Based on the resources available, the role of the Planning Group will be to ensure optimal implementation of the main framework in the form of shorter-term (annual or bi-annual) work plans, including the possibility of time-limited financial support to countries when required. As 12 countries are already engaged in such a collaborative effort with WHO, many of the proposed approaches can be readily piloted.

Relationship with industry

Representatives from vaccine-manufacturer organizations are contributors to the implementation of the Global Vaccine Safety Initiative. In addition, there is an expectation that systems will be established to facilitate interaction between national governments, multilateral agencies and manufacturers. CIOMS is an international, nongovernmental, nonprofit organization which was established jointly by WHO and UNESCO in 1949. Its main objectives are: to facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary; to maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO, and to serve the scientific interests of the international biomedical community in general.⁵⁴ Because of its unique position, CIOMS, with assistance from involved stakeholders, is to provide a forum for discussion and exchanges between regulators, national representatives and industry, in order to further the global targets described in Objective 8.

New collaborators

Organizations and other groups committed to vaccine safety, which have not so far been part of the Blueprint process, are encouraged to become a part of this initiative. WHO welcomes all who share the vision, mission and values of the Blueprint initiative, to help contribute to the achievement of its objectives.

⁵⁴ Council for International Organizations of Medical Sciences (http://www.cioms.ch/about/frame_about.htm).

Annex:

What is an adverse event following immunization (AEFI)?

General definition

Adverse event following immunization (AEFI): Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Cause-specific definitions

- 1) Vaccine product-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
- 2) Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device, as provided by the manufacturer.
- 3) Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus, by its nature, is preventable.
- 4) Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization.
- 5) Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

Department of Immunization, Vaccines and Biologicals

Family, Women's and Children's Health (FWC)

World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

E-mail: vaccines@who.int

Web site: <http://www.who.int/immunization/en/>